Associations of Cancer Mortality With Halomethanes in Drinking Water [1]

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ABSTRACT—Associations between site- and sex-specific county cancer mortality rates and levels of trihalomethanes (THM's) in drinking water were examined after adjustment of rates for the influence of multiple socioeconomic, industrial, and demographic factors. U.S. counties with sampled supplies were grouped by percent of the county population receiving water from the supply, as well as by region of the country. For two sites (bladder and lung), county rates were also adjusted for the activity level in specific high-risk industries. Positive correlations with THM levels were observed for several cancers, including bladder and brain cancers in both sexes, and non-Hodgkin's lymphoma and kidney cancer in males. Stomach cancer in females showed a negative association. Bladder cancer mortality rates showed the strongest and most consistent association with a THM exposure index, after control for differences in social class, ethnic group, urban versus rural residence, region of the United States, and industrialization of the county. These ecologic associations suggested that further evaluation in analytic investigations is warranted.—J Natl Cancer Inst 61: 979-985, 1978.

Chloroform ($CHCl_3$) and BTHM, present in drinking water from municipal treatment plants, arise largely from the interaction of chlorine with organic precursors and bromide ion in untreated raw water and, in a few areas, from contamination of source waters by industrial outfalls (*1, 2*). THM are widely found at concentrations ranging from less than one part to several hundred parts per billion, usually at much higher levels than other halogenated hydrocarbon contaminants (*3, 4*). Disinfection by chlorination has been used in most large U.S. cities with surface water supplies since the early 20th century (*5*).

$CHCl_3$ produces tumors in rats and mice when administered in large repeated doses (*6*). Other halogenated hydrocarbons identified in drinking water are carcinogenic in laboratory animals, and BTHM are mutagenic in standard bacterial test strains (*7*). These observations, and results from geographically based correlational studies in humans (*8, 9*), have led to concern that THM and other halogenated organics in treated drinking water may be carcinogenic when ingested over long periods.

Adequate assessment of possible risks has been hampered by differences in industrial, socioeconomic, and demographic risk factors between populations exposed to various concentrations of THM and by the lack of prior specification of the types of cancer likely to be involved. Measurement of THM levels in two 1975 surveys of municipal drinking water supplies provided the opportunity to generate hypotheses about specific cancers after control for a number of such risk factors.

METHODS

Age-standardized cancer mortality rates by site and sex in whites for the years 1968–71 were calculated by the direct method, with the 1960 total population used as the standard. This was done for the 923 U.S. counties greater than 50% urban in 1970. The numbers of deaths, according to county of usual residence of the decedent, were obtained from the National Center for Health Statistics. Population estimates, demographic data, and numbers of workers in various industries for these counties were obtained from the U.S. Bureau of the Census. The percent of a county's population served by the major municipal water supply was estimated by dividing the population served in 1960 (*10*) by the county population. $CHCl_3$ and TTHM levels in each water supply were obtained from two surveys conducted by EPA in 1975: NORS (*3*) and a survey conducted in EPA's Region V (*4*). Levels of BTHM were derived by subtraction, after concentrations were converted to moles per liter. Data from the first and second rounds of EPA's 1976 NOMS were used to investigate the reproducibility of the 1975 data (*11*).

A weighted linear regression model was used to predict sex- and site-specific cancer rates in the 923 U.S. counties over 50% urban in 1970. For each county, the weight was directly proportional to the square root of the county's person-years at risk and hence inversely proportional to the standard deviation of the estimated mortality rate. The following county level predictor variables were in the regression model: percent urban (1970); median school years completed by persons over age 25 (1970); population size (1970); ratio of 1970 to 1950 population; percent work force in

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ABBREVIATIONS USED: BTHM=bromine-containing trihalomethane(s); EPA=U.S. Environmental Protection Agency; NOMS=National Organic Monitoring Survey; NORS=National Organics Reconnaissance Survey; THM=trihalomethane(s); TTHM=total trihalomethane(s).

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manufacturing (1970); and percent foreign stock in each of 10 ethnic groups (Asian, Canadian, Eastern European, Finnish, German, Mexican, Northern European, Russian, Scandinavian and Southern European) (1970). An indicator variable giving the county location in one of nine geographic regions was also used.

A predicted age-adjusted, site-specific cancer rate among whites was calculated for each of the 923 counties, for each anatomic site having a sex-specific mortality rate greater than 1.5/100,000/year (table 1). The residual mortality rate (difference between the observed and the predicted rates) was then compared to the measured THM level (as the logarithm) by use of the bivariate correlation coefficient as a measure of association. This part of the analysis was restricted to the 76 (of the 923) counties, or subsets of them, in which more than half of the population was served by a sampled water supply. Correlation coefficients were weighted by the square root of the sex-specific years at risk in the population served by a single supply, estimated by the product of percent of population served and population at risk. We also performed a subsidiary analysis in which the multiple regression to generate residuals, and the subsequent bivariate correlations, were weighted directly by the population-years at risk.

TABLE 1.—*Average annual age-adjusted mortality rates per 100,000 population, by sex, in U.S. counties greater than 50% urban,[a] 1968–71*

Anatomic site or type of cancer	ICD Code[b]	Mortality rate/100,000/year	
		Males	Females
Buccal cavity	141, 143–146, 148	4.03	<1.5
Esophagus	150	4.54	<1.5
Stomach	151	10.31	5.10
Colon	153	18.86	16.14
Rectum	154	6.82	3.93
Liver	155.0, 155.1	1.53	<1.5
Gallbladder	156.0	<1.5	1.69
Pancreas	157	10.81	6.54
Lung	162	57.65	11.42
Melanoma	172	2.04	<1.5
Breast	174	<1.5	27.67
Cervix	180	—	5.21
Uterus	182	—	4.46
Ovary	183.0	—	9.27
Prostate gland	185	17.49	—
Urinary bladder	188	7.16	2.10
Kidney	189.0	4.27	1.93
Brain & other nervous system	191, 192	5.13	3.39
Lymphosarcoma & reticulum cell sarcoma	200	4.30	2.89
Hodgkin's disease	201	2.17	<1.5
Multiple myeloma	203	<1.5	1.64
Leukemia	204, 205, 206	6.92	4.35
All sites combined	140–209	196.07	131.63

[a] A total of 923 counties, by U.S. Bureau of the Census definition.
[b] International Classification of Disease designation (8th revision).

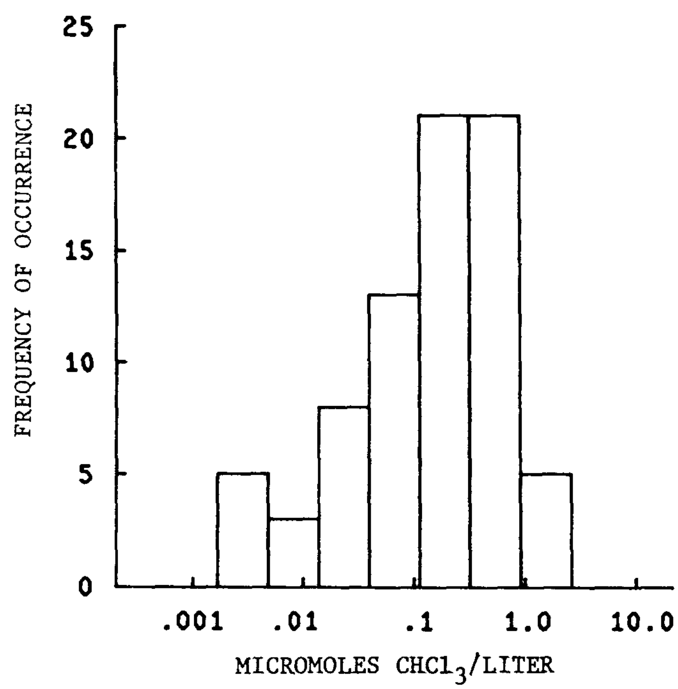
In further analyses, partial correlation coefficients were calculated after controlling for the effect of the percent of the population employed in specific high-risk industries on residual mortality rates. This was done for two sites (bladder and lung) with known or suspected industrial determinants for cancer after a positive association with THM had been observed. Partial correlation coefficients were also calculated for bladder cancer residual rates with a THM exposure variable after controlling for lung cancer residual mortality rates.

For one site, i.e., bladder, sex-specific mortality rates in the 76 counties were also regressed in a model weighted by the square root of population-years at risk against a reduced set of predictor variables and the logarithm of the THM level.

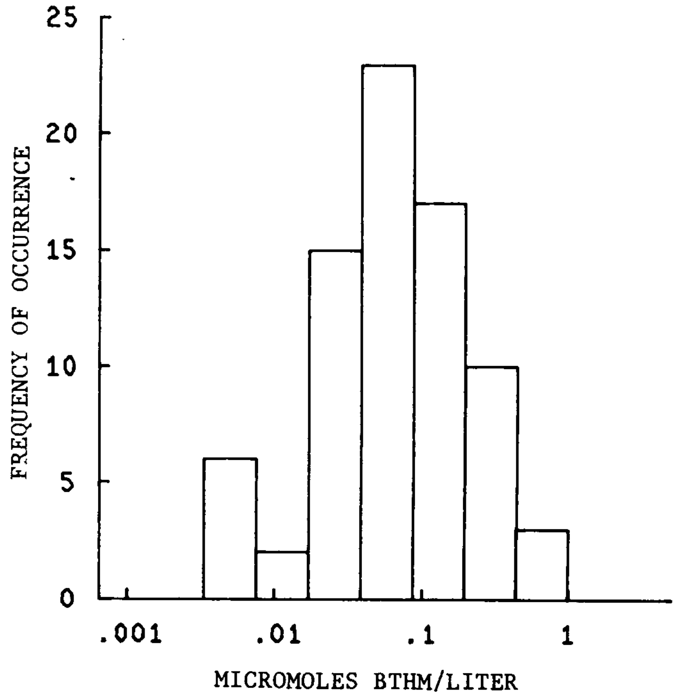
RESULTS

Exposure Indexes

The distributions of $CHCl_3$ and BTHM in the 76 areas of this study are shown in text-figures 1 and 2. The three THM indicators used ($CHCl_3$, BTHM, and TTHM) were highly correlated with one another. Correlation coefficients between the log-transforms of their respective concentrations in the 76 areas were: $CHCl_3$ and BTHM, $r=0.54$; $CHCl_3$ and TTHM, $r=0.93$; and BTHM and TTHM, $r=0.74$ ($P>0.001$ for each correlation). BTHM was comprised mostly of bromodichloromethane and chlorodibromomethane. Some supplies also had measurable levels of bromoform (*3, 4*).



TEXT-FIGURE 1.—Frequency distribution of $CHCl_3$ levels in 76 U.S. drinking water supplies. The *abscissa* is linear in the logarithm of the level.



TEXT-FIGURE 2.—Frequency distribution of BTHM levels in 76 U.S. drinking water supplies. The *abscissa* is linear in the logarithm of the level.

The correlation coefficient between 1975 NORS chloroform levels (as the logarithm) and the concentrations measured in each of the first two rounds of the 1976 NOMS (*12*) in the 42 supplies common to both were 0.73 and 0.90 ($P<0.001$). Corresponding Spearman rank correlations were 0.78 and 0.88.

Cancer Mortality

Tables 2 and 3 show correlation coefficients between residual cancer mortality rates and the logarithm of one of three THM indicators in counties grouped according to the percent of the county population served by a sampled water supply ("high," "intermediate," or "low percent-served counties"). These coefficients were from calculations weighted by the square root of the population-years at risk. The criterion used to select anatomic sites for presentation was that the two-tailed *P*-value of the correlation coefficient between a residual rate and at least one of the three THM indicators be less than 0.2 in the high percent-served counties (85–100%, No.=25) or in the total group (50–100%, No.=76). Cancers with different results between sexes included cancers of lung and stomach, which met the criterion in females but not in males, and those of kidney and brain and non-Hodgkin's lymphoma, which met the criterion in males but not in females.

The correlation coefficients between residual rates and each of the three THM indicators followed similar patterns, due to the strong association between indicators. As an example, table 4 shows the correlation coefficients of residual bladder cancer rates with each

TABLE 2.—*Correlation coefficients between residual mortality rates in white males and THM levels in drinking water, by percent of the county population served by the sampled supply*

Site or type of cancer	THM indicator	Correlation coefficients[a] for counties in which the percent population served was:			
		50–64[b]	65–84[c]	85–100[b]	50–100[d]
Pancreas	$CHCl_3$	0.04 (0.83)	−0.06 (0.77)	−0.32 (0.12)	−0.13 (0.27)
Prostate gland	$CHCl_3$	0.34 (0.10)	0.03 (0.87)	0.30 (0.14)	0.17 (0.14)
Bladder	BTHM	−0.22 (0.29)	0.29 (0.15)	0.38 (0.06)	0.19 (0.10)
Kidney	$CHCl_3$	−0.16 (0.44)	−0.11 (0.60)	0.42 (0.04)	0.07 (0.55)
Brain	BTHM	0.10 (0.65)	0.18 (0.37)	0.24 (0.25)	0.17 (0.14)
Non-Hodgkin's lymphoma	BTHM	−0.33 (0.11)	−0.19 (0.36)	0.36 (0.08)	−0.03 (0.81)
Stomach[e]	TTHM	0.01 (0.96)	0.05 (0.81)	−0.14 (0.49)	−0.02 (0.87)
Pancreas[e]	BTHM	−0.12 (0.57)	−0.31 (0.12)	0.04 (0.84)	−0.16 (0.18)
Lung[e]	TTHM	−0.02 (0.94)	0.02 (0.90)	0.15 (0.46)	0.07 (0.56)

[a] *P*-value for two-tailed *t*-test is shown *in parentheses.*
[b] No.=25.
[c] No.=26.
[d] No.=76.
[e] Included for comparison with results for females (table 3), for whom stronger associations in high percent-served counties were observed.

TABLE 3.—*Correlation coefficients between residual mortality rates in white females and THM levels in drinking water, by percent of the county population served by the sampled supply*

Site or type of cancer	THM indicator	Correlation coefficients[a] for counties in which the percent population served was:			
		50–64[b]	65–84[c]	85–100[b]	50–100[d]
Stomach	TTHM	0.01 (0.97)	−0.11 (0.59)	−0.36 (0.07)	−0.16 (0.17)
Pancreas	BTHM	−0.31 (0.13)	−0.12 (0.56)	0.31 (0.14)	−0.03 (0.82)
Lung	TTHM	0.25 (0.23)	0.28 (0.17)	0.15 (0.46)	0.22 (0.05)
Bladder	BTHM	−0.01 (0.97)	0.21 (0.30)	0.45 (0.02)	0.21 (0.06)
Pancreas[e]	$CHCl_3$	−0.25 (0.22)	0.20 (0.32)	−0.06 (0.77)	0.02 (0.85)
Kidney[e]	$CHCl_3$	−0.33 (0.11)	0.19 (0.37)	−0.04 (0.83)	−0.01 (0.96)
Brain[e]	BTHM	−0.07 (0.73)	−0.03 (0.90)	0.19 (0.35)	0.04 (0.72)
Non-Hodgkin's lymphoma[e]	BTHM	−0.36 (0.08)	0.26 (0.20)	−0.04 (0.83)	0.01 (0.97)

[a] *P*-value for two-tailed *t*-test is shown *in parentheses.*
[b] No.=25.
[c] No.=26.
[d] No.=76.
[e] Included for comparison with results for males (table 2), for whom stronger associations in high percent-served counties were observed.

TABLE 4.—*Correlation coefficients between residual bladder cancer mortality rates and levels of three THM indicators in drinking water, in 25 U.S. counties having 85–100% of their population served by the measured supply*

Sex	Statistical measurement	THM indicator		
		$CHCl_3$	TTHM	BTHM
Males	r	0.23	0.30	0.38
	P[a]	0.26	0.14	0.06
	95% confidence interval of r	$-0.18 \leq r \leq 0.57$	$-0.11 \leq r \leq 0.62$	$-0.02 \leq r \leq 0.67$
Females	r	0.25	0.38	0.45
	P[a]	0.24	0.06	0.02
	95% confidence interval of r	$-0.16 \leq r \leq 0.59$	$-0.02 \leq r \leq 0.67$	$0.08 \leq r \leq 0.72$

[a] From a two-tailed t-test.

of the three THM indicators for the high percent-served counties. When more than one THM indicator met the criterion, the indicator with the strongest association with site-specific residual rates was presented.

Bladder cancer residual mortality in both sexes showed a strong correlation with BTHM. The associations for each sex in high percent-served counties were stronger than those in intermediate counties, which in turn were stronger than the associations in low percent-served areas. The correlation coefficient of bladder cancer residual mortality with log-BTHM (by sex and percent-served county group) showed only small changes after residual lung cancer mortality rates were partialled out of the association. In low, intermediate, and high percent-served counties, the partial correlation coefficients in males were −0.23, 0.32, and 0.33, respectively. The partial correlation coefficients for females were 0.02, 0.14, and 0.42.

The associations with bladder cancer were also observed when bladder cancer mortality rates were regressed against socioeconomic, industrial, and demographic variables along with the THM levels in all 76 study counties. This multiple regression approach was not applied to subsets of the 76 counties because of the large number of predictor variables in the regression model.

Brain cancer in males and females showed a positive association with BTHM in high percent-served counties (r=0.24 and r=0.19, respectively). For males, successively weaker correlations were detected in intermediate and low percent-served counties (r=0.18 and r=0.10, respectively). The coefficients for females were lower in the intermediate and low than in the high percent-served counties, but a decreasing gradient was not present. Stomach cancer residual mortality rates in females were negatively associated with log-TTHM in high (r=−0.36) and intermediate percent-served counties (r=−0.11). For males, the correlation with stomach cancer was weak and negative in high percent-served counties (r=−0.14) and negligible in intermediate and low percent-served counties. The correlation between THM levels and pancreatic cancer rates showed opposite trends in the sexes. In high percent-served counties, pancreatic cancer in females was positively correlated with BTHM (r=0.31) and in males the correlation with $CHCl_3$ was negative (r=−0.32). Lung cancer residual mortality rates in females were correlated with TTHM in each of the three county groups, with no clear pattern in the relative strength of the association from low to high percent-served counties. Lung and kidney cancer and non-Hodgkin's lymphoma displayed elevated coefficients in the high percent-served counties in males only. No trends were noted in intermediate and low percent-served groupings. Prostate cancer mortality rates showed a correlation with log-$CHCl_3$ levels in high and low percent-served counties but a negligible association in intermediate counties.

When counties with extreme values of site- and sex-specific residual mortality rates (>3 SD from the mean value) were removed from the analyses, the recalculated correlation coefficients changed little, with the exception of those for stomach cancer in females. For stomach cancer in females, removal of one county each from the high and intermediate percent-served groups decreased the negative correlation coefficient with TTHM from −0.36 to −0.28 and from −0.11 to −0.01, respectively. Removal of the two counties from the total (No.=76) group changed the correlation coefficient from −0.16 to −0.08.

When the regression model and subsequent bivariate correlations were weighted by the unmodified population-years at risk, results generally followed the patterns of association described above. Several correlation coefficients for males were of lower magnitude, but coefficients for bladder, kidney, and brain cancer residual mortality rates retained their significance. Patterns of correlation in females showed little change, and two additional sites, brain and ovary, showed interesting associations with log-BTHM. Correlation coefficients for these sites in low, intermediate, and high percent-served and in all study counties were, respectively: brain, r=0.17, 0.17, 0.26, and 0.17; ovary, r=0.03, 0.15, 0.31, and 0.16.

Counties Grouped by Region

Tables 5 and 6 show the correlation coefficients, calculated as described previously, in counties grouped by region of the country (North, South, and Mountain Pacific). Only counties in which 65% or more of the population were served by a single water supply were included, due to the uneven distribution among regions of counties with 50–64% served. The disproportionate number of Northern counties arises from inclusion of 34 counties from EPA's Region V survey

TABLE 5.—*Correlation coefficients between residual mortality rates in white males and THM levels in drinking water, by region of the United States*

Site or type of cancer	THM indicator	Correlation coefficients[a] for regions of the United States: North[b]	South[c]	Mountain Pacific[d]	All regions[e]
Pancreas	$CHCl_3$	−0.07 (0.71)	−0.24 (0.44)	−0.14 (0.76)	−0.16 (0.26)
Prostate gland	$CHCl_3$	0.01 (0.94)	0.29 (0.34)	0.24 (0.60)	0.15 (0.31)
Bladder	BTHM	0.52 (0.002)	0.04 (0.90)	−0.02 (0.96)	0.30 (0.03)
Kidney	$CHCl_3$	0.11 (0.54)	−0.11 (0.73)	0.66 (0.11)	0.14 (0.33)
Brain	BTHM	0.30 (0.10)	0.01 (0.98)	0.11 (0.81)	0.20 (0.16)
Non-Hodgkin's lymphoma	BTHM	0.06 (0.74)	0.08 (0.79)	0.05 (0.92)	0.06 (0.70)
Stomach[f]	TTHM	0.15 (0.42)	−0.44 (0.13)	−0.07 (0.89)	−0.02 (0.87)
Pancreas[f]	BTHM	−0.13 (0.47)	−0.15 (0.63)	−0.41 (0.36)	−0.17 (0.24)
Lung[f]	TTHM	0.24 (0.19)	−0.03 (0.91)	−0.08 (0.86)	0.09 (0.52)

[a] *P*-value for two-tailed *t*-test is shown *in parentheses*. Counties with at least 65% of their population served by one water supply were included in this analysis.
[b] No.=31.
[c] No.=13.
[d] No.=7.
[e] No.=51.
[f] Included for comparison with results for females.

covering Ohio, Indiana, Illinois, Michigan, Wisconsin, and Minnesota.

Bladder cancer in females was positively correlated with levels of BTHM in all three regions (r=0.30, 0.20, and 0.63). In males, the correlation was strong in Northern counties (r=0.52) but essentially zero in the other regions [r=0.04 (South) and −0.02 (Mountain Pacific)]. Brain cancer residual mortality rates in males and females were positively correlated with log-BTHM in all regional groups, but strengths of the associations were variable. Stomach cancer rates in females were negatively correlated with log-TTHM in the three regions, with high values in the South and Mountain Pacific (r=−0.57 and −0.43). In males, the association with stomach cancer was uneven, being negative in one region and of small magnitude in the others. The correlation of pancreatic cancer with haloform levels showed opposite patterns in males and in females, following the pattern observed when counties were grouped by percent of the population served. In each of the three regions, the association in males (with log-$CHCl_3$) was negative, but in females (with log-BTHM) it was positive. Lung cancer residual rates in both sexes showed uneven associations with log-TTHM in counties grouped by region. A correlation for this site was observed for females, but not males, in Southern counties (r=0.45). Non-Hodgkin's lymphoma in males was weakly correlated with log-BTHM in the three regions, and in females, the correlation for this site was strong in Mountain Pacific counties but not in others.

Residual kidney cancer mortality rates generally were correlated across regions with log-$CHCl_3$ concentrations, but uneven patterns of association were observed in both sexes. A strong association in males was observed in Western counties but not in other regions. The correlation coefficient between prostate cancer mortality rates and log-$CHCl_3$ was elevated in Southern and Western counties, but absent in Northern counties.

Adjustment for High-Risk Industries

To evaluate possible confounding of occupational exposures in the association of THM with bladder cancer mortality, we calculated the correlation coefficients between log-BTHM and residual bladder cancer mortality rates after partialling out the effect of association of the rates with the percent of the population employed in industries that have been associated with this cancer. This was done in counties with at least 65% of the population served by one water supply (No.=51). High-risk industries included those with standard industrial classification codes for the rubber, chemical, and leather industries (*13*). The partial correlation coefficients were 0.33 (P=0.01) for females and 0.31 (P=0.01) for males, essentially unchanged from the unadjusted values.

A parallel analysis was performed for lung cancer, by use of log-TTHM as the exposure index and the use of paper, chemical, petroleum, and transportation indus-

TABLE 6.—*Correlation coefficients between residual mortality rates in white females and THM levels in drinking water, by region of the United States*

Site or type of cancer	THM indicator	Correlation coefficient[a] for regions of the United States: North[b]	South[c]	Mountain Pacific[d]	All regions[e]
Stomach	TTHM	−0.06 (0.75)	−0.57 (0.04)	−0.43 (0.34)	−0.23 (0.10)
Pancreas	BTHM	0.14 (0.45)	0.22 (0.48)	0.07 (0.87)	0.09 (0.51)
Lung	TTHM	0.16 (0.40)	0.45 (0.12)	−0.37 (0.41)	0.22 (0.11)
Bladder	BTHM	0.30 (0.11)	0.20 (0.51)	0.63 (0.13)	0.33 (0.02)
Pancreas[f]	$CHCl_3$	0.33 (0.07)	0.10 (0.75)	−0.47 (0.29)	0.08 (0.58)
Kidney[f]	$CHCl_3$	−0.16 (0.38)	0.22 (0.48)	0.29 (0.52)	0.08 (0.59)
Brain[f]	BTHM	0.01 (0.95)	0.12 (0.69)	0.31 (0.50)	0.09 (0.56)
Non-Hodgkin's lymphoma[f]	BTHM	−0.08 (0.67)	0.29 (0.33)	0.87 (0.01)	0.11 (0.43)

[a] *P*-value for two-tailed *t*-test is shown *in parentheses*. Counties with at least 65% of their population served by one water supply were included in this analysis.
[b] No.=31.
[c] No.=13.
[d] No.=7.
[e] No.=51.
[f] Included for comparison with results for males.

tries, due to reported associations (*14*). Partial correlation coefficients between lung cancer residual mortality rates and log-TTHM, after adjusting for percent employed in these industries, were 0.22 for females (P=0.05) and 0.07 for males (P=0.58), essentially the same as the unadjusted coefficients of 0.22 and 0.09.

DISCUSSION

When it is recognized that humans have been widely exposed to a class of chemical compounds over a long period, and moreover, when specific members of the class are identified as carcinogens or mutagens in laboratory tests, appropriate epidemiologic risk assessment should be made. A number of problems arise in planning such studies. Important among these is deciding which anatomic sites of cancer to investigate, because animal tests are not always reliable predictors of the human sites that might be involved. One approach is to first conduct descriptive human studies to specify hypotheses that may then be analytically tested in further investigations.

Such a dilemma occurred with the recognition that THM occur widely in drinking water supplies, are carcinogenic in laboratory animals, and are mutagenic in bacterial tester strains. We therefore used data from the first systematic surveys of THM in municipal water supplies to generate hypotheses for subsequent testing. Thus we evaluated the data for consistency of associations after analysis in several ways, rather than relying solely on the statistical significance of our findings. Specifically, we investigated associations between THM levels and mortality rates for a number of cancer sites after appropriate control for possible confounding variables. We checked the stability of observed associations by seeing the influence of removing extreme values as well as by using an alternative weighting scheme in the analyses. Furthermore, we looked for associations that were present in both sexes and across geographic regions and that gave some evidence of a dose-response relationship based on both proportion of the exposed populations in the geographic units chosen for study and the measured levels of THM.

When the data are regarded in this manner, bladder cancer clearly stands out as warranting further study. Reasonably strong associations between bladder cancer and THM levels in drinking water appear in both sexes after control for differences in social class, ethnic group, urban versus rural residence, and overall county industrialization. Further analyses indicate that specific high-risk industries for bladder cancer do not confound this association, nor is it confounded by lung cancer rates, a possible surrogate for levels of cigarette smoking. In addition, the association occurs among females at approximately the same level in all three geographic regions. The only inconsistency in the analysis of this association is among males, where the correlation is restricted to the Northern region. It is noteworthy that due to the numbers of counties involved, the Northern region yields the most stable estimates of association in this study.

Brain cancer also gives sufficient evidence of an association to warrant future consideration. The association of residual brain cancer mortality rates and BTHM levels is present for both sexes and, in general, decreases in magnitude from high, to intermediate, to low percent-served areas. However, the associations are not as strong as those for bladder cancer and there is variation between regions. Because little is known about the etiology of brain cancer in humans, these associations may be important clues for further study. Some credibility for this opinion is also lent by studies indicating that occupational exposure to organic chemicals may induce brain tumors (*15, 16*).

For other sites, the inconsistencies in the associations generally outweigh the consistencies. Three sites, however, should be mentioned. There is some evidence of an association between $CHCl_3$ levels and kidney cancer, restricted to males. This observation is consistent with results from animal studies, which show a greater sensitivity of the male than the female kidney to the toxic effects of $CHCl_3$, including carcinogenesis (*17*). Lung cancer rates show associations in females only. We were unable to control for cigarette smoking, the most important risk factor for lung cancer, which has a greater impact on disease rates among males than among females. Inasmuch as the lung provides an important excretory route for several low-molecular-weight halogenated compounds (*18*), the correlation in females opens the possibility that cancers of this site may be associated in a causal manner with THM exposure. Finally, non-Hodgkin's lymphoma is associated with THM levels in males but not in females, and appears in only the high percent-served counties. The pattern across regions is uneven. However, this association may warrant further pursuit, because a similar observation was made in a correlational study of cancer mortality and drinking water quality in the Ohio River basin (*19*), and other work suggests that persons exposed to chemical agents may be at high risk for cancers of the lymphoid system (*20, 21*).

Although we have attempted to control for a number of possible sources of error in our analyses, potential problems remain. This is a descriptive study, in which we used exposure and disease information from aggregates of people rather than from individuals. As is usually true in this type of study, there is a possibility that we have identified some associations and failed to identify others simply because of inadequate control for confounding variables. We have attempted to control for such factors as social class, urbanization, ethnicity, and industrialization. The measures of these factors are crude, however, and several other variables on which we have no direct information (e.g., cigarette smoking, diet) are also potentially important. Control for variables not included and/or finer control for the included ones may produce different results. Indeed, the results from this study give a clear demonstration of the need for attempts to control for other relevant variables. Fairly strong associations existed between THM levels and colon cancer rates in both sexes and lung cancer rates in males prior to the inclusion of the

10 foreign stock predictor variables in the model. Without the control for ethnicity, both of these tumors also showed some evidence of a dose-response relationship with the proportion of the population exposed. Similarly, strong negative correlations between THM levels and stomach cancer rates were noted for both sexes prior to control for the ethnic composition of the population. Our rather crude attempts at such control removed the association in males and considerably weakened it in females. Finer control (e.g., age-specific information about ethnicity) might reasonably be expected to eliminate the association in females also.

Another major area of concern is how well current environmental measurements reflect past exposures. THM measures for each supply came from only a few grab samples of drinking water. With the long latency of cancers of environmental origin, it is important to know how accurately these measures reflect past exposures. Comparison of the levels of $CHCl_3$ used in this study with measurements made a year later indicates a high level of consistency in the ranking of different water supplies. This implies that the major factors causing differences in THM levels *(22)* vary less within one supply than between supplies, at least over the short term. Of the supplies in the study, all were chlorinating in 1975 *(3)*, and all but a few were disinfecting with chlorine in 1949 *(23)*.

Although the problems with these data, and descriptive studies in general, should not be minimized, we believe that this investigation has served well our intended purpose of hypothesis generation.

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